amount of a pharmaceutical composition comprising a DNA damaging compound] a brain tumor or a breast tumor.

Please add the following new claim:

-- 33. (New) The method according to claim 24, wherein the herpesvirus is HSV-1. --

REMARKS

I. Status of the Claims

Claims 1-27 are pending in the application. Claims 29-32, drawn to a non-elected invention, have been canceled. Claims 1-27 stand rejected under 35 U.S.C. §112, first paragraph, 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-27 are rejected, and the specification is objected to, as the disclosure allegedly lacks enabling support for the claimed invention. The examiner has raised a number of different, and quite distinct, objections to the specifications and claims. Applicants seek to address each of the examiner's concerns as they apply to the amended claims. A discussion of each point identified by applicants is presented below.

Limitation Regarding Vectors - According to the examiner, the specification is "severely limited" in the use of HSV strains R3616 and R899-6. The claims have been amended to recite "herpesvirus." This is believed to narrow the scope of the claims in such a way as to address the examiner's concerns (see Office Action at page 3, lines 13-21).

Dosage and Methods of Administration - The examiner has alleged that there are no dosages given in the specification. This is incorrect. The specification discusses virus input at page 9, lines 17-20, page 13, line 11, page 24, lines 5-9, page 28, lines 17-18, page 31, lines 10-12 and original claim 19. With respect to methods of administration, it should be noted that each of the independent claims recites that the herpesvirus is either contacted with the tumor cells or delivered to the tumor or tumor site. Thus, the claim itself, while not limiting the specific ***manner*** in which this occurs, contains an assurance that the herpesvirus reaches its target. Thus, it is believe that this concern also has been addressed.

Use of Cytokines - Applicants believe that this rejection has been overcome by the amendments to certain claims, in particular, those to claims 13-16. Again, it is emphasized that each of the independent claims recites delivery of two agents -- a herpesvirus and ionizing radiation. The use of TNFα (or a TNFα gene) merely is an additional embodiment that will augment the response resulting from the primary agents, and is not required, as illustrated by the use of a non-TNFα-containing vector. Thus, the entire discussion of "other cytokines" appears inapposite here.

Establishing a Mechanism of Action - The examiner takes issue with the claims on the grounds that the specification does not establish, for the TNFα construct, what causes the effect. Applicants submit that identification of a mechanism of action is not necessary for patentability. And, as stated above, the use of TNFα is not a prerequisite to the present invention, it merely is a particular embodiment. Thus, it is submitted that the claimed invention, which involves the use of herpesvirus and ionizing radiation, is enabled regardless of the possible additional effect of TNFα in certain dependent embodiments.

Gene Therapy Generally - The examiner concludes the rejection with a discourse of the limitations of gene therapy. However, the claims do not recite "gene therapy" except in dependent aspect where the enablement is provided by the broader embodiment of herpesvirus plus ionizing radiation. Thus, it is believed that this entire discussion is not relevant given the amendment of the claims to recite herpesviral infection, coupled with ionizing radiation. Nonetheless, applicants nonetheless feel compelled to comment on the content of this section. The "reasons" given by the examiner in support of the rejection do not constitute grounds for non-enablement. Rather, the action sets forth "reasons" to doubt the very ***foundation and credibility*** of gene therapy. Thus, the examiner's position, even if stated as a enablement rejection, is really one of utility. As such, applicants must traverse the rejection on the grounds that gene therapy is neither incredible nor without foundation. Though the examiner has identified several pessimistic reviews of gene therapy, there are a number of positive results, including clinical trials, that show gene therapy to be a viable endeavor. Thus, to the extent that this rejection has any relevance here, applicants submit that it is improper as a matter of law.

If there is any point that applicants have failed to discuss, applicants' representative would be please to entertain any questions from the examiner following his review of the response. In the absence of any questions, applicants respectfully submit that the rejection of the amended claims under §112, as well as the objection to the specification, are unwarranted; reconsideration and withdrawal thereof are requested.

III. Rejection Under 35 U.S.C. §102

Claims 1-3, 6, 8, 9, 12, 23-25 and 27 are allegedly anticipated by Fujiwara *et al.* ("Fujiwara"). Fujiwara is said to disclose adenoviral-mediated transfection of cancer cells prior to administration of a DNA damaging composition. Applicants have amended the claims to address the examiner's concerns. In particular, each of the claims now recites herpesvirus administration and either implicitly or explicitly the additional administration of ionizing radiotherapy. Because Fujiwara does not disclose herpesviruses, applicants submit that the rejection is overcome. Reconsideration and withdrawal is respectfully requested.

IV. Rejection Under 35 U.S.C. §103

Claims 1-27 are rejected as obvious over Wills *et al.* ("Wills"), taken with Fujiwara and Boviatis. Wills is cited as teaching the development and characterization of recombinant adenoviruses encoding p53 for cancer gene therapy. Wills also is said to introduce the concept of combining gene therapy with ionizing radiotherapy. Fujiwara is cited further as disclosing the combination of chemotherapeutics with p53 therapy. Boviatis is cited as disclosing the suitability of HSV and retrovirus, in addition to adenovirus, in gene therapy. And finally, the examiner alleges that it was well known, at the time of filing, that

adenovirus infections alone could cause host cell destruction via an immune response against adenoviral products.

As stated above, applicants have amended each of the independent claims to set forth two elements. First, applicants methods each set forth the combination of (i) ***herpesvirus infection*** and (ii) ***ionizing radiation***. This combination is not taught or suggested by any of the references. Thus, the rejection is believed to be overcome. Second, both Wills and Fujiwara rely on provision of p53, which is not part of the presently claimed invention. Third, only Boviatis mentions herpesvirus, but it is nowhere indicated in the references that herpesviruses should be substituted in a combined therapy protocol as presently claimed.

Fourth, it should be pointed out that the references all describe the use of viral vectors for the purpose of ***gene*** therapy, *i.e.*, for the delivery of a therapeutic gene to a cell. The present invention, as now more clearly claimed, describes a completely different phenomenon -- the ability of herpesviruses and ionizing radiation to cooperate in cell killing. No gene delivery is required - only infection and radiation. Though recited in a various ways in each of the pending independent claims, the inventor's unique observation is at the basis of each claim. More importantly, it is a concept that is missing from each of the cited references.

And fifth, applicants point out that while an immune response against a viral antigen may have some beneficial effect, there is nothing in the prior art that would suggest using viral vectors generally, much less herpesviruses specifically, in a combined therapeutic approach as set forth in the claims as amended. For this additional reason, the rejection now is improper.

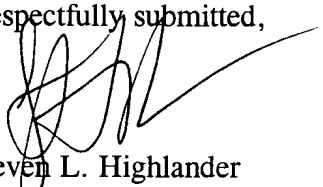
And fifth, applicants point out that while an immune response against a viral antigen may have some beneficial effect, there is nothing in the prior art that would suggest using viral vectors generally, much less herpesviruses specifically, in a combined therapeutic approach as set forth in the claims as amended. For this additional reason, the rejection now is improper.

In light of the foregoing, applicants submit that the cited references, alone or in combination, fail to obviate the invention as now claims. Reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

In light of the foregoing amendments and remarks, applicants respectfully submit that all claims are in condition for allowance and solicit and early indication to that effect. Should Examiner Milne have any questions regarding this response, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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